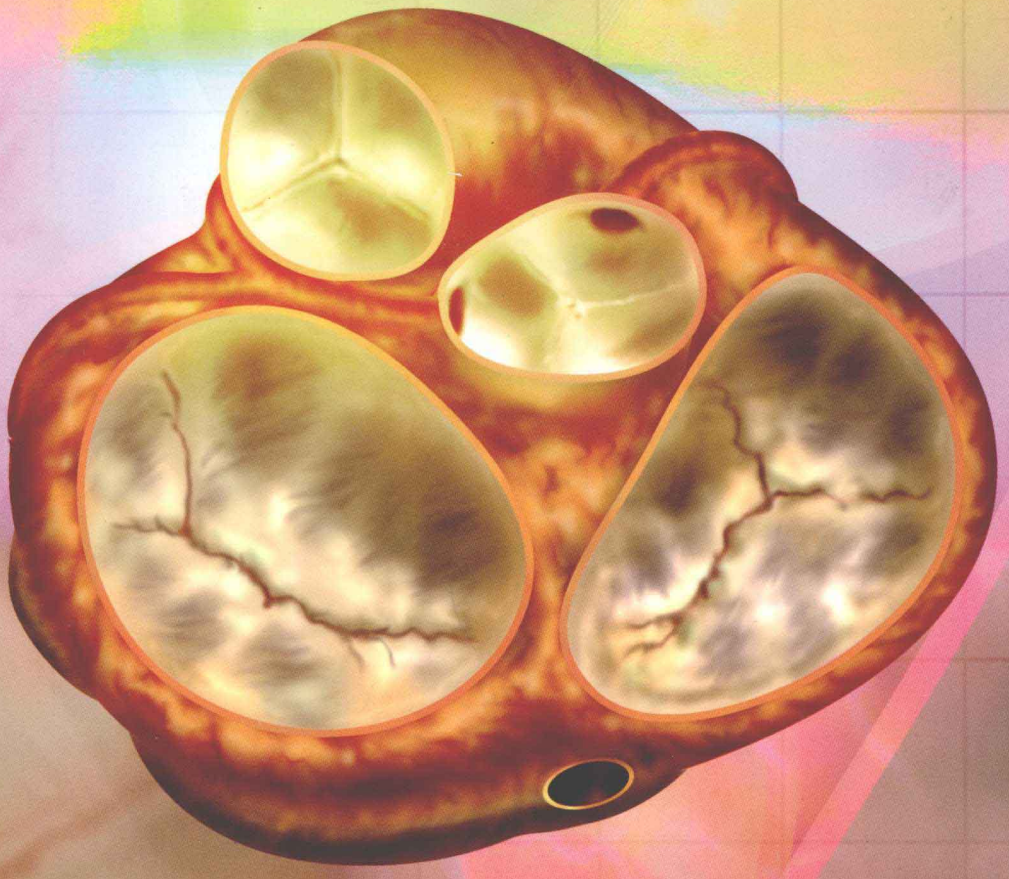
OTTO & BONOW

# VALVULAR HEART DISEASE

## A Companion to BRAUNWALD'S HEART DISEASE



THIRD EDITION

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Third Edition


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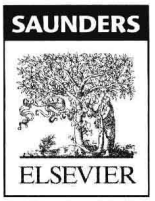

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VALVULAR HEART DISEASE:
A COMPANION TO BRAUNWALD'S HEART DISEASE

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# Valvular Heart Disease

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# Preface

Worldwide, valvular heart disease remains a major cause of morbidity and mortality. In the United States, there are approximately 100,000 open-heart operations each year for valve replacement or repair, which accounts for about 20% of all cardiac surgical cases. A far greater number of patients have valve disease that is managed medically. Because the prevalence of valve disease increases as a function of age, we anticipate that even greater numbers of patients will come to medical attention with the aging of the population in this country and abroad.

Recognition of a heart murmur remains central to the practice of medicine because primary care physicians usually make the initial diagnosis of valvular heart disease followed by referral to a specialist. Noninvasive methods for diagnosis and evaluation of disease severity have greatly increased our knowledge of valvular heart disease: the ability to monitor stenosis severity with varying flow rates has broadened our understanding of the complex hemodynamics of valvular stenosis and regurgitation; serial noninvasive studies in patients with mild or moderate degrees of valve dysfunction have improved our understanding of the natural history of valvular disease; and these noninvasive methods now allow precise assessment of the changes in valvular and ventricular function after medical or surgical interventions. In addition, better options for correction of valve dysfunction, including percutaneous interventions, improved valve substitutes, and the increasing use of valve repair procedures now are available. Earlier intervention is increasingly being considered as the risk-benefit ratio improves and as the potential long-term adverse consequences of valve disease are more clearly defined.

Optimal care of the patient with valvular heart disease requires knowledgeable collaboration among several different types of health professionals. The diagnosis often is suspected by the primary care physician or nurse practitioner based on auscultation of a cardiac murmur or recognition of symptoms that might be due to valvular disease. Further evaluation by a cardiologist typically involves subspecialists in echocardiography and interventional cardiology, as well as the skilled assistance of cardiac sonographers, radiology technicians, and cardiac catheterization laboratory technologists. Cardiac surgeons expert in valve repair or replacement have made enormous advances in the past two decades that have transformed the outlook of patients with valve disease. In patients undergoing surgical or percutaneous intervention, cardiovascular anesthesiologists, cardiac perfusionists, and coronary care unit nurses are all key members of the team. Increasingly, cardiac surgeons and interventional cardiologist are working together to decide on the optimal treatment plan in each patient, with the increasing use of "hybrid" approach where a combination of surgical and nonsurgical techniques are used in an procedure suite designed for both open surgical or robotic and percutaneous procedures. In addition, optimal management of patients with valvular heart disease often depends on close collaboration with other medical specialties, for example, high-risk obstetrics in the pregnant patient with valvular heart disease, medical genetics in patients with inherited conditions, electrophysiologists when arrhythmias complicate the clinical presentation, and the heart transplant team in patients with irreversible ventricular dysfunction.

This book integrates the diverse knowledge required for optimal care of the patient with valvular heart disease by each of these health professionals. Since the publication of the second edition of Otto's *Valvular Heart Disease*, there have been substantial advances in our understanding of the disease processes and optimal treatments for valvular heart disease, with an upsurge of interest in understanding the causes of valve disease and improved diagnostic techniques. With publication of updated guidelines by the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology, evidence-based approaches to the treatment of valvular heart disease are becoming accepted. We anticipate more clinical outcome studies in patients with valvular heart disease in the future. This field has now matured to the point where a multi-author book, building on the material in the second edition, and inclusion as part of the Braunwald Companion Series is appropriate.

The authors for each chapter were chosen for their clinical and research expertise, although we acknowledge that there now are many other experts in valvular heart disease worldwide who could not be included in this volume due to space limitations. Each chapter provides a summary of the pathophysiology, clinical presentation, and natural history of the disease process along with a discussion of medical therapy and timing of surgical intervention, including postoperative outcome. Each chapter is extensively illustrated and the major clinical trials are summarized in tables whenever possible. Current guidelines are provided and discussed in each chapter, with an appendix providing the exact definitions of the recommendation grades and levels of evidence used in the ACC/AHA guideline documents. The reference list for each chapter emphasizes more recent studies, with only the most important earlier studies cited.

The book begins with a section on basic principles in diagnosis and management of valvular heart disease. Chapters discuss disease prevalence and anatomic pathology followed by an in-depth chapter on our rapidly expanding knowledge of the cellular and molecular mechanisms of disease initiation and progression. A chapter on the left ventricular response to pressure and/or volume overload is included as this is a key factor in the decision-making process regarding the optimal timing of surgical intervention. Next are several chapters on diagnostic evaluation of valvular heart disease by echocardiography, cardiac catheterization, and advanced cardiac imaging techniques. The chapter on basic principles of medical management in patients with valvular heart disease serves as a quick clinical reference source with tables summarizing indications for echocardiography and timing of follow-up studies, diagnosis and prevention of rheumatic fever, updated endocarditis guidelines, recommendations for physical activity in patients with valve disorders, an overview of anticoagulation recommendations, and indications for coronary angiography.

The next section of the book addresses aortic valve disease and includes chapters on aortic stenosis, aortic regurgitation, the bicuspid aortic valve, and both surgical and percutaneous approaches to treatment of aortic valve disease. The section on mitral valve disease includes separate chapters on rheumatic valve disease, myxomatous mitral valve disease, functional mitral regurgitation, timing of surgery for mitral

regurgitation, mitral valve repair and replacement, and percutaneous approaches to mitral valve dysfunction. The final section of the book covers several topics, including intraoperative echocardiography, right-sided valve disease, endocarditis, prosthetic valves, valve disease in children, and management of valvular heart disease during pregnancy.

While every attempt has been made to provide accurate and up-to-date information, medicine is an ever-changing field, so readers always should check the recent literature for any changes in diagnostic approaches or therapy. The number of new publications in the area of valve disease is so large that not all could be included in the cited references in this book. It is expected that the interested reader will use electronic databases to find additional references as needed. In addition, professional organizations such as the AHA, ACC, and European Society of Cardiology periodically develop consensus guidelines for patient management and the latest update of those guidelines should be consulted. Chapters on specific diagnostic techniques and surgical and percutaneous interventions are provided as background information. Of course, expertise in these areas requires appropriate education and experience as defined by the relevant accreditation and credentialing bodies and professional organizations.

Valvular heart disease historically has been an interest for physicians and continues to be an area of fascination for many of us, with the initial stimulus for learning often being the appreciation of a cardiac murmur on physical examination as a medical student. Now that we are on the verge of understanding the cellular and molecular mechanisms of valve disease, it is important to consolidate our current knowledge in order to focus on the possibility of preventing disease initiation and progression in the future. An improved understanding of the mechanisms of disease, combined with well-designed clinical outcomes trials, will lead to even more advances in prevention and treatment of valvular heart disease in the future.

CATHERINE M. OTTO, MD

ROBERT O. BONOW, MD

# Foreword

Valvular heart disease is an important clinical problem, responsible for an estimated 20,000 deaths and 100,000 hospitalizations each year in the United States alone. Although it has been recognized for centuries, in recent decades valvular disease has been caught in two important cross-currents. The first is demographic. Despite the recent decline in the prevalence of rheumatic heart disease in North America, Western Europe, and Australia, the total number of patients with valvular heart disease in these regions is rising steadily because of the increase in degenerative valvular diseases that accompanies the aging of the population. The numbers of patients with valvular heart disease in developing countries is rising particularly rapidly because the incidence of new cases of rheumatic heart disease has not (yet) fallen to the low levels observed in the developed nations, while the number of the elderly and the accompanying degenerative valve diseases are increasing.

The second important cross-current relates to the changes in the diagnosis and management of valvular heart disease. Until relatively recently, the cardiac catheterization laboratory was the site at which the diagnosis and functional assessment of valvular heart disease were obtained, while the management of advanced valvular disorders took place in the operating room. Now, noninvasive imaging techniques—echocardiography, including three-dimensional echocardiography, as well as cardiac magnetic resonance imaging and computed tomography—all provide rich anatomic and functional information. The cardiac catheterization laboratory is becoming increasingly the site of catheter-based correction of valvular disorders. This approach began 25 years ago with balloon mitral valvuloplasty and now involves growing efforts to perfect correction of severe mitral regurgitation and transcatheter insertion of prosthetic aortic valves.

The editors of *Valvular Heart Disease*, Drs. Otto and Bonow, are among the world's leaders in this field. They have selected outstanding authors, each an authority in the particular area that they cover. They cover in depth the cross-currents mentioned above, which make the understanding and management of valvular heart diseases much more dynamic than ever. They also cover systematically the pathogenesis, pathophysiology, clinical findings, imaging, natural history, and therapeutic options. We congratulate the editors and authors for their important contributions and welcome this excellent book to our growing list of *Companions to Heart Disease*. We anticipate that this text will become the standard in this important field.

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# Acknowledgments

Sincere thanks are due to the many individuals who helped make this book a reality. In particular, we would like to thank the chapter authors for their time and efforts in providing excellent chapters. Some of the chapters in this edition include material from the second edition of *Otto's Valvular Heart Disease* with the full knowledge and consent of Catherine Otto, the author of the previous chapters.

Finally, as always, we would like to thank our families for their constant encouragement and support.

# Contents

CHAPTER 1



# The Burden of Valvular Heart Disease

George A. Mensah

## KEY POINTS

- The dramatic decline in the incidence of acute rheumatic fever has led to a corresponding reduction in rheumatic valve disease in most industrialized nations. Nevertheless, nearly 16 million people worldwide live with rheumatic heart disease, and an estimated 233,000 deaths are attributable to rheumatic fever or rheumatic heart disease each year.
- The reduction in rheumatic valve disease has not resulted in a decrease in valvular heart disease burden because increasing life expectancy in many countries and a continuing epidemic of atherosclerotic risk factors have led to an increase in age-related and degenerative valvular heart disease.
- Mild to moderate degrees of valvular heart disease are relatively common in adults, increase in prevalence with advancing age, and are associated with reduced survival.
- Sclerosis of the aortic and mitral valves, even in the absence of hemodynamic obstruction, is associated with increased cardiovascular mortality.
- Hospitalization for symptom management and valve repair or replacement constitutes the major morbidity, and heart failure is the major sequela leading to death. An estimated 20,260 deaths and 100,000 hospitalizations for valvular heart disease occur in the United States annually.
- Procedures for repair or replacement of heart valves more than doubled in the United States in the last two decades with an increasing preference for bioprosthetic over mechanical valves.
- Health disparities in access to care and quality of care for valvular heart disease exist by age, gender, race/ethnicity, and socioeconomic status. Continued investments in strategies to improve health care quality for all and eliminate these disparities are necessary.

Diseases and disorders of the heart valves constitute a major worldwide cause of disability, reduced quality of life, and premature mortality from cardiovascular diseases. Throughout most of the 19th and early 20th centuries, rheumatic fever and consequent rheumatic valvulopathy were the leading causes of valvular heart disease worldwide and remain so today in most developing countries where rheumatic fever remains the leading cause of heart disease in children and young adults.[1] In most industrialized nations, however, the dramatic decline in the incidence and sequelae of rheumatic fever coupled with significant increases in life expectancy and prevalence of persons aged 65 years and older has led to a changing etiology and an increasing burden of age-related valvular heart disease. In addition, a better understanding of valvular biology and pathophysiology, improved diagnostic imaging, and novel approaches to valve repair and replacement in most developed countries have contributed to improved patient survival and an increasing prevalence of valvular heart disease.[2,3]

In this chapter, the changing etiology of valvular heart disease is first reviewed. The overall burden of valvular heart disease, together with the incidence, prevalence, natural history, and clinical outcomes of aortic, mitral, tricuspid, and pulmonary valve diseases and their sequelae are then presented. The epidemiology of multivalvular and mixed valvular heart disease is also reviewed. Endocarditis and associated morbidity and mortality are discussed. Disease burden in women of reproductive age is then reviewed. Trends in heart valve procedures and the epidemiology of prosthetic valve dysfunction are then presented. Finally, disparities in access to quality health care in the prevention, treatment, and the control of valvular heart disease are reviewed.

## A CHANGING ETIOLOGY

Valvular heart disease may be congenital, acquired, or both (as in progressive calcification of a congenitally bicuspid aortic valve or endocarditis of a congenitally malformed mitral leaflets). Acquired valvular heart disease may be of rheumatic or nonrheumatic origin. Until the mid-20th century, the predominant etiology of acquired valvular heart disease worldwide was rheumatic, a nonsuppurative cardiovascular sequela of group A streptococcal pharyngitis.[4] Although a dramatic decline in the incidence of rheumatic fever and rheumatic

heart disease has been observed in industrialized nations over the past five decades, rheumatic fever and rheumatic heart disease remain major clinical and public health problems in developing countries where their most devastating effects are on children and young adults in their most productive years.[4] In developing countries, the majority of cases of rheumatic valve disease affect the mitral valve, with mitral stenosis (MS) being the most common lesion in adults, but aortic and tricuspid valve involvement may be seen as well. In children aged 5 years and younger, mitral regurgitation (MR) is the most common cardiac manifestation in developing countries, and obstructive valve disease is distinctly rare in this age group.[5]

In their recent analysis of the global burden of group A streptococcal diseases, Carapetis et al[6] estimated a worldwide rheumatic heart disease prevalence of 15.6 million people, with 470,000 new cases of rheumatic fever and 233,000 deaths attributable to rheumatic fever or rheumatic heart disease each year. Table 1-1 shows the estimated number of deaths and disability adjusted life years lost to rheumatic heart disease in 2000 by World Health Organization regions.[4] As shown in Figure 1-1, almost all of these cases and deaths occur in developing countries, with the highest calculated regional prevalence of the disease among children noted in sub-Saharan Africa (5.7 per 1000), the Pacific and indigenous populations in Australia and New Zealand (3.5 per 1000), and south central Asia (2.2 per 1000).[6] In fact, as many as half of the 2.4 million children affected by rheumatic heart disease globally reside in Africa alone.[7]

In many countries in these regions, more than 50% of patients with rheumatic heart disease are unaware of the diagnosis and, thus, do not receive secondary prophylaxis for prevention of recurrent rheumatic fever. The prevalence of diagnosed rheumatic heart disease in many countries in which echocardiographic imaging is not available may represent a significant underestimation of the true burden of disease.[8] Marijon et al[8] recently showed that systematic screening with echocardiography reveals as much as a 10-fold greater prevalence of rheumatic heart disease, compared with clinical screening in the same population.[8] Both the primary episode of rheumatic fever and the long-term valvular sequelae lead to substantial medical costs for this potentially preventable disease. Recognizing the huge burden of morbidity and mortality from rheumatic heart disease in Africa and the availability of cost-effective and relatively inexpensive

**TABLE 1–1 The Global Burden of Rheumatic Heart Disease: Estimated Number of Deaths and Disability Adjusted Life Years Lost to Rheumatic Heart Disease in 2000, by World Health Organization (WHO) Region**

| | Deaths | | DALYs Lost | |
|---|---|---|---|---|
| WHO Region | n ($\times 10^3$) | Rate (per 100,000 population) | n ($\times 10^3$) | Rate (per 100,000 population) |
| Africa | 29 | 4.5 | 0.77 | 119.8 |
| The Americas | 15 | 1.8 | 0.24 | 27.4 |
| Eastern Mediterranean | 21 | 4.4 | 0.59 | 121.6 |
| Europe | 38 | 4.3 | 0.49 | 56.1 |
| Southeast Asia | 117 | 7.6 | 2.66 | 173.4 |
| Western Pacific | 115 | 6.8 | 1.78 | 105.4 |
| World | 332 | 5.5 | 6.63 | 109.6 |

DALYs, disability adjusted life years.

From World Health Organization: Rheumatic fever and rheumatic heart disease. World Health Organ Tech Rep Ser 2004;923:1–122, with permission.

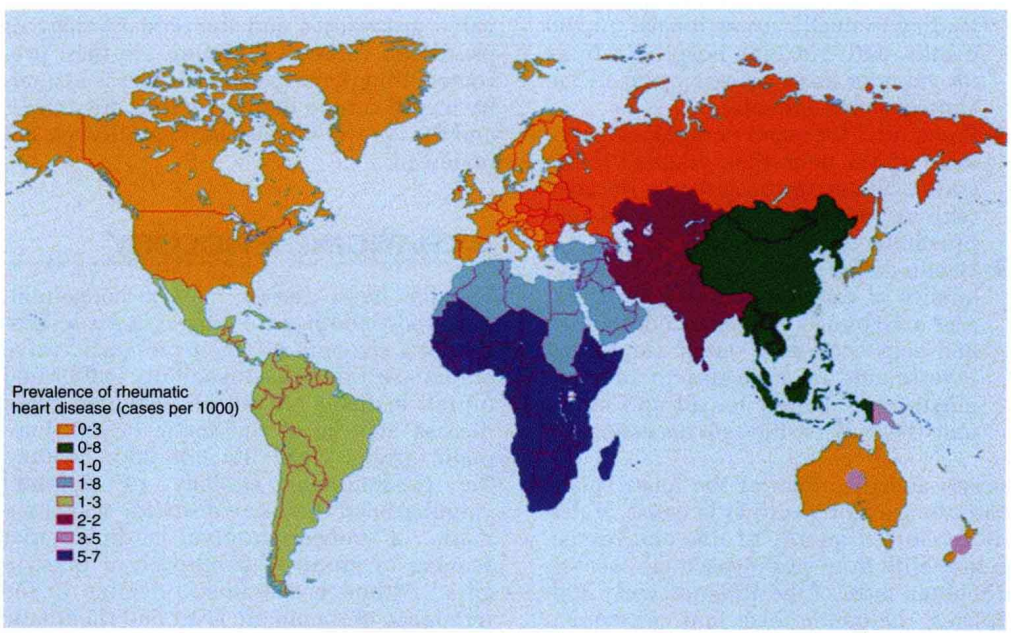


**FIGURE 1–1** The worldwide prevalence (cases per 1000) of rheumatic heart disease in children aged 5-14 years. *(From Carapetis JR, Steer AC, Mulholland EK, Weber M: The global burden of group A streptococcal diseases. Lancet Infect Dis 2005;5:685-694, with permission.)*

interventions for prevention and control, a recent initiative (the Drakensberg Declaration) called for a comprehensive program using awareness, surveillance, advocacy, and prevention to eliminate rheumatic fever and rheumatic heart disease in the region.[7,9]

In sharp contrast to the picture in developing countries, the incidence of acute rheumatic fever has dramatically declined in most developed countries to less than 1 per 100,000.[4] This has resulted in a dramatic decline in the incidence of rheumatic valve disease in developed countries. The overall burden of valvular heart disease has, however, not declined because of an increase in age-related degenerative valve disease.[10-14] This pattern is expected to persist as life expectancy continues to improve and the proportion of persons aged older than 65 years increases significantly in developed nations.

For example, from 1950 to 2005, the total resident population of the United States increased from 151 to 296 million, representing an average annual growth rate of 1.2%. During that same period, however, the population aged 65 years and older grew, on average, 2.0% per year, increasing from 12 to 37 million, and the population aged 75 years and older more than quadrupled from 4 to 18 million persons. Current projections suggest that the population aged 75 years and older will continue to increase to 12% in 2050.[15] As a result of increasing life expectancy and continuing decline of rheumatic fever incidence, nonrheumatic and age-related degenerative valvular heart disease will predominate in developed countries.

In addition to the increasing life expectancy and declining incidence of acute rheumatic fever, the continuing epidemic of major cardiovascular risk factors is likely to contribute to the changing etiology of valvular heart disease. Several studies have now shown that valve calcification, typically seen in age-related valvular heart disease, is the result of an active process that is preceded by basement membrane disruption, inflammatory cell infiltration, lipid deposition, neurohormonal influence, and endothelial dysfunction.[16-20] This process is associated with diabetes, hypercholesterolemia, hypertension, and tobacco use and thus is likely to be exacerbated and adversely impact the prevalence of valvular heart disease in the setting in which these risk factors are suboptimally controlled.[16,21] In addition, adverse changes in the synthetic, morphologic, and metabolic functions of the valvular endothelial cells contribute to progressive age-related valvulopathy[22] Thus, in the setting of uncontrolled cardiovascular risk factors and a continuing epidemic of obesity and diabetes, the epidemiologic burden of valvular heart disease is likely to increase.[14,23-27]

## NONRHEUMATIC VALVULAR HEART DISEASE

The worldwide burden of nonrheumatic valvular heart disease in the population has not been estimated. Two recent publications provide data on the U.S. experience at the population and community levels[28] and the European experience in a survey of clinical patients (the Euro Heart Survey).[29] In the U.S. experience, Nkomo et al[28] pooled three population-based studies to obtain data for 11,911 randomly selected adults from the general population who had been assessed prospectively with echocardiography. They also analyzed data from a community study of 16,501 adults who had been assessed using clinically indicated echocardiography.

From the population-based studies, they estimated a national prevalence of valvular heart disease, corrected for age and sex distribution from the U.S. 2000 population, to be 2.5%. The prevalence of moderate or severe valvular heart disease increased with age, from 0.7% in 18 to 44 year olds to 13.3% in the 75 years and older group. No significant sex-related differences were noted. In the community group, valve disease was diagnosed in 1505 (1.8% adjusted) adults and disease frequency increased considerably with age, from 0.3% of the 18 to 44 year olds to 11.7% of those aged 75 years and older, but was diagnosed less often in women than in men (odds ratio 0.90, 0.81 to 1.01; $P = 0.07$).[28] Importantly, the adjusted mortality risk ratio associated with valve disease was 1.36 (1.15 to 1.62; $P = 0.0005$) in the population and 1.75 (1.61 to 1.90; $P < 0.0001$) in the community. These findings suggest that moderate or severe valvular diseases are relatively common in the United States, that their prevalence increases with age (Figure 1-2), and that they are associated with significantly reduced survival (Figure 1-3).[28]

The Euro Heart Survey on valvular heart disease prospectively included 5001 outpatients or hospitalized patients from 92 centers in 25 European countries. All patients had to have echocardiographic evidence of primary and significant valvular heart disease and, as such, the survey cannot inform us of the population burden of valve disease in Europe.[29] However, it provides very useful information on the spectrum of valve disease in this population, overall management, and survival. Native valve disease was present in 71.9% with the remaining 28.1% having undergone previous valve surgery.[29] Aortic stenosis (AS) and MR were the most common native valve disorders (34% and 25%, respectively) and were mostly caused by degenerative diseases (the mean age was 69 and 65 years, respectively). Multivalvular disease was present in 20% of the patients and at least one comorbidity was noted in 36.3% of the patients. A major contribution from this sur-

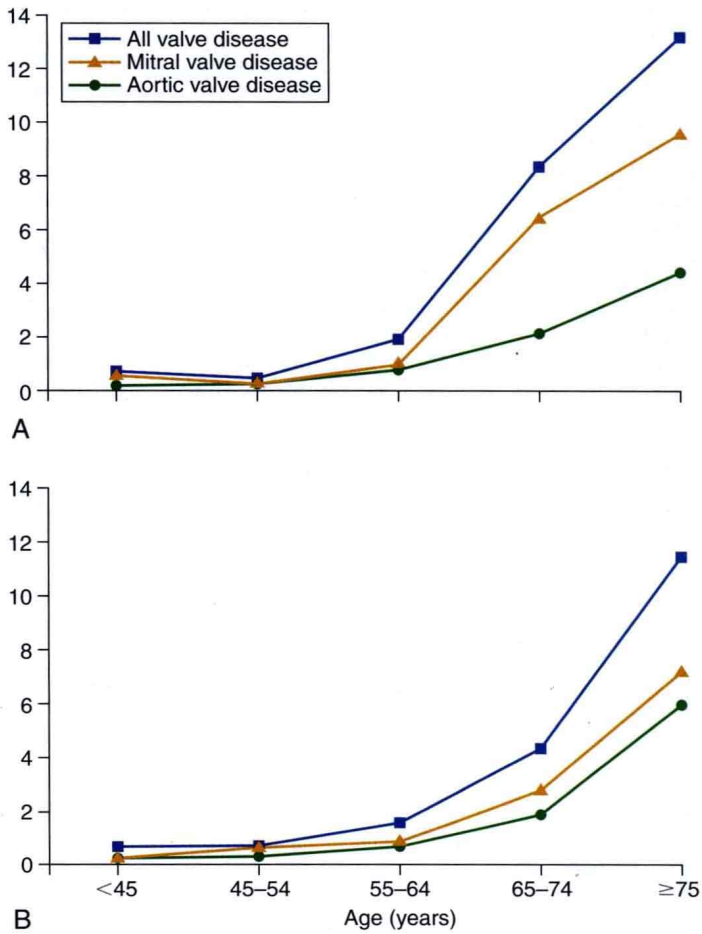


**FIGURE 1–2** The prevalence of valvular heart disease in the United States. Frequency in (**A**) population–based studies and (**B**) in the Olmsted County community. *(From Nkomo VT, Gardin JM, Skelton TN, et al: Burden of valvular heart diseases: A population–based study. Lancet 2006;368:1005-1011, with permission.)*